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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,806	04/18/2001	Sudhir Agrawal	HYZ-069CN (47508-407)	8489

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S-4.

Office Action Summary	Application No.	Applicant(s)	
	09/837,806	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11,14-16,18-26 and 29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11,14-16,18-26 and 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-15-04, 9-24-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-15-04.

Claims 1, 4-11, 14-16, 18-26 and 29-39 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Applicant's arguments filed 4-15-04 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 15, and 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting HIV-1 or HIV-2 infection in a cell in vitro comprising contacting the cell with an anti-gag specific antisense oligonucleotide, does not reasonably provide enablement for inhibiting HIV infection in a cell in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of inhibiting HIV-1 or HIV-2 infection in a cell comprising contacting the cell with a 21 nucleobase oligonucleotide specifically complementary to a consecutive 21 nucleobase portion of SEQ ID NO: 5, and which nucleotides within the oligonucleotide are linked via phosphorothioate internucleotide linkages, and at least two 2'-substituted 5'-terminal ribonucleotides.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Copies of these references were provided in a prior Office action, mailed 8-28-02. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found

more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-

327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting HIV-1 or HIV-2 infection in an organism. The specification teaches methods of orally administering antisense oligonucleotides modified for enhanced bioavailability that specifically target gag of HIV. One skilled in the art would not accept on its face the examples given in the specification of orally administering antisense, whereby bioavailability is enhanced due to the incorporation of phosphorothioate internucleotide linkages and due to the incorporation of 2'-O-alkyl groups into the oligonucleotide, or examples in the art of the in vitro inhibition of HIV infectivity comprising the administration in vitro of anti-gag antisense, as being correlative or representative of the successful inhibition of HIV in an organism comprising the administration of antisense, in view of the lack of guidance in the specification and known unpredictability associated with in vivo inhibition of a target gene in an organism whereby HIV infection is inhibited in target cells in that organism.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to compositions and methods of inhibiting HIV-1 or HIV-2 infection in a cell comprising contacting the cell in vivo with an anti-gag antisense oligonucleotides. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or

tissues harboring HIV-1 or HIV-2 whereby HIV replication and infection is inhibited in cells in vivo. Since the specification fails to provide any particular guidance for the targeting and inhibition of appropriate target cells harboring HIV or susceptible to HIV-1 or HIV-2 infection, whereby expression of gag is inhibited in the appropriate target cells in an organism and HIV infection is inhibited, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 5, 8 and 9 are rejected under 35 U.S.C. 102(a) or (e) as anticipated by Agrawal et al.

Agrawal et al (USPN 5,591,721) teach synthetic oligonucleotides 21 nucleobases in length specifically complementary to nucleotides 324-345 of HIV-1 gag of SEQ ID NO: 5, and pharmaceutical compositions thereof, which

oligonucleotides comprise SEQ ID Nos: 1 and 3, and which oligonucleotides are linked via phosphorothioate internucleotide linkages, and further comprise at least two 5' and/or 3'-terminal ribonucleotides comprising 2'-O-methyl moieties (See especially col. 7-9, Table 1; SEQ ID No: 1). Agrawal et al also teach the administration of these oligonucleotides, and their physiological stability following oral administration (see especially col. 12-14; and claim 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5-11, 14-16, 18-26, 29-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al as applied to claims 1, 4, 5, 8 and 9 above, and further in view of Hovanessian et al and Goodchild et al insofar as the claims are drawn to compositions and methods of inhibiting HIV-1 or HIV-2 infection in a cell comprising the in vitro administration of oligonucleotides 21 nucleobases in length specifically complementary to nucleotides 324-345 of HIV-1 gag of SEQ ID NO: 5, which oligonucleotides comprise SEQ ID Nos: 1 and 3, and which oligonucleotides are linked via phosphorothioate internucleotide linkages, and further comprise at least two 5' and/or 3'-terminal ribonucleotides comprising 2'-O-methyl moieties.

Agrawal et al is relied upon as cited in the 102 rejection above.

Agrawal et al also teach the physiological stability of an array of 2'-O-alkyl oligonucleotides following oral administration (see especially table 1 in col. 7-8). This array includes oligonucleotides comprising between one and twenty-five 2'-O-substituted ribonucleotides, including four 5'- and 3'-terminal 2'-O-alkyl ribonucleotides flanking at least 13 deoxynucleotides (see sequence No. 10 in table 1).

Agrawal et al do not teach the in vitro inhibition of HIV-1 or HIV-2 infection comprising the administration of antisense oligonucleotides. Agrawal et al do not explicitly teach oligonucleotides comprising four 3'- or 5'-terminal 2'-O-alkyl ribonucleotides, flanking 13 deoxynucleotides, nor their stability in systemic plasma following oral or intravenous administration.

Goodchild et al (USPN 4,806,463) teach compositions and methods for inhibiting HIV infections in vitro comprising the administration of antisense oligonucleotides specifically targeting the HIV gag gene (see especially columns 4-6, example 3 in columns 10-13; claims 4 and 5).

Hovanessian et al (USPN 5,470,702) teach homology between HIV-1 and HIV-2 nucleic acids encoding HIV proteins and polypeptides (see especially col. 1 and col. 6-7).

It would have been obvious to one of ordinary skill in the art to incorporate numerous 2'-O-alkyl ribonucleotides on the 5' and 3'-termini of antisense oligonucleotides to enhance oligonucleotide stability from nuclease degradation because Agrawal et al teach an increase in oligonucleotide stability from exonuclease degradation upon incorporation of 2'-O-alkyl groups sequentially onto the 5'- and 3'-termini of the oligonucleotides. One of ordinary skill in the art would have expected increased stability of these modified oligonucleotides in systemic plasma because Agrawal et al teach the stability of modified oligonucleotides in the hostile environments of the stomach and intestine up to six hours after oral administration, as well as teaching the absorption of up to 20% of total oligonucleotides ingested (e.g. see especially col. 12). One of ordinary skill in the art would therefore have expected that the stability of oligonucleotides administered intravenously would be even greater than those introduced through the more hostile route of oral administration, because it was well known in the art that increased antisense degradation occurs following oral administration compared to intravenous administration. It would have been

obvious to one of ordinary skill in the art to utilize antisense oligonucleotides of 21 nucleobases in length, and which sequences (i.e. of SEQ ID Nos: 1-4 of the instant invention) target the gag HIV-1 and HIV-2 gene in vitro in order to inhibit HIV infection in vitro including HIV-1 and HIV-2 infections in vitro because Goodchild et al teach the in vitro inhibition of HIV using antisense specifically targeting HIV gag. And Goodchild teach nucleotide sequence homology of gag in the various HIV strains, including HIV-1 and HIV-2. The homology between HIV gag was well known in the art at the time the invention was made compared to the highly variable nucleotide sequences encoding the HIV envelope proteins in the different HIV strains, and elaborated in the teachings of Goodchild. One of ordinary skill in the art would have been motivated to provide anti-gag antisense oligonucleotides for inhibiting HIV-1 or HIV-2 because these forms of virus are known to infect and deleteriously affect human cells. One of ordinary skill in the art would have expected that the incorporation of 2'-O-alkyl and phosphorothioate modifications into oligonucleotides would enhance their stability and target binding, thereby enhancing their inhibitory effects in vitro on expression of the known gag target gene. One of ordinary skill in the art would have expected that the in vitro inhibition of gag expression by antisense, including the instantly claimed antisense of lengths of 21 nucleobases, would lead to the in vitro inhibition of HIV-1 and HIV-2 replication in vitro, because the success of antisense inhibition of HIV in vitro had been demonstrated previously by Goodchild et al and the similarities between HIV-1 and HIV-2 nucleic acid sequences including gag had been taught previously by Hovanessian et al. One

of ordinary skill in the art would have been motivated to incorporate phosphorothioate internucleotide linkages, ribonucleotides at the 5' and 3' termini, and 2'-O-modifications within the ribonucleotides at the 5' and 3' termini of antisense oligonucleotides, including at the 5' and 3' termini and in at least 2 residues per termini, because it had been taught previously by Agrawal et al that the incorporation of such modifications into ribonucleotide termini protect the stability of antisense oligonucleotides from nuclease degradation. One of ordinary skill in the art would have expected that antisense oligonucleotides comprising these modifications would provide enhanced target gene inhibition because of their enhanced stability, and because it had been known in the art that such modifications as phorphorothioate internucleotide linkages enhances target binding and cellular uptake of oligonucleotides. And one of ordinary skill in the art would have expected that the specific targeting and inhibition of HIV gag expression would inhibit HIV infection, because it had been taught previously by others including Goodchild et al that the inhibition of gag expression in HIV leads to the inhibition of HIV infectivity of human cells harboring HIV in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

6-7-04

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